KBG syndrome presenting with brachydactyly type E

Renata Libianto
Kathy H.C Wu
Sophie Devery
John A. Eisman

The University of Notre Dame Australia, john.eisman@nd.edu.au

Jackie R. Center

Follow this and additional works at: https://researchonline.nd.edu.au/med_article

Part of the Medicine and Health Sciences Commons

This other contribution to a refereed journal was originally published as:

Original other contribution to a refereed journal available here:
https://doi.org/10.1016/j.bone.2019.03.012

This other contribution to a refereed journal is posted on ResearchOnline@ND at https://researchonline.nd.edu.au/med_article/1030. For more information, please contact researchonline@nd.edu.au.
Title:
KBG Syndrome Presenting with Brachydactyly Type E

Authors:
Renata Libianto1-3, Kathy Wu4-7, Sophie Devery4, John Eisman1,2,6,8, Jackie Center1,2,6,8

Affiliations:
1 Bone Division, Garvan Institute of Medical Research, Sydney
2 Department of Endocrinology, St Vincent’s Hospital Sydney
3 Department of Medicine, The University of Melbourne
4 Clinical Genomics Unit, St Vincent’s Hospital Sydney
5 Discipline of Genetic Medicine, University of Sydney
6 School of Medicine, UNSW Sydney
7 Genomics and Epigenetics Division, Garvan Institute of Medical Research, Sydney
8 School of Medicine Sydney, University of Notre Dame Australia

Corresponding author:
Dr Renata Libianto
Bone Division, Garvan Institute of Medical Research
384 Victoria St, Darlinghurst
NSW 2010, Australia
rlibianto@gmail.com
(612) 8382 1111

Conflict of interest:
The authors declare no conflict of interest
Abstract
We report the case of a young woman who presented at age 10 years with height on the tenth centile, brachydactyly type E and mild developmental delay. Biochemistry and hormonal profiles were normal. Differential diagnoses considered included Albright hereditary osteodystrophy without hormone resistance (a.k.a pseudopseudohypoparathyroidism), 2q37 microdeletion syndrome and acrodysostosis. She had a normal karyotype and normal FISH of 2q37. Whole genome sequencing (WGS) identified a mutation in the ANKRD11 gene associated with KBG syndrome. We review the clinical features of the genetic syndromes considered, and suggest KBG syndrome be considered in patients presenting with syndromic brachydactyly type E, especially if short stature and developmental delay are also present.

Keywords
KBG syndrome; ANKRD11 gene; skeletal disorder, brachydactyly type E
Case

The patient initially presented at age 10 years with brachydactyly and mild developmental delay. Investigations at the time revealed general shortening of metacarpals and metatarsals, especially of the 4th and 5th digits, as well as advanced bone age (12 years at chronological age of 10.5 years). No specific diagnosis was made and she was lost to follow-up.

She represented at age 24 years to an Endocrinologist and subsequently to a Clinical Geneticist, due to ongoing uncertainty regarding the diagnosis and a renewed interest by the patient. Her medical history was reviewed and included a clavicular fracture after falling off a mattress as a toddler; childhood jaw surgery to correct mandibular protrusion; lower limb length discrepancy requiring the use of orthotics since late-teens, and depression. She underwent menarche at the age of 10 years and continued to have regular menstrual cycles. She was taking citalopram for anxiety/depression and an oral contraceptive pill for dysmenorrhoea.

She was born after a normal pregnancy and delivery, with birth weight, length and head circumference all within the average range. She was delayed in her developmental milestones and required extra support in a mainstream school for specific learning difficulties. She completed high school and went on to obtain a nursing certificate.

Her parents are non-consanguineous and of Caucasian background. An older sister had a short distal phalanx of the thumb and a repaired atrial septal defect. Two other siblings are apparently normal. There is a strong family history of osteoporosis affecting her mother, two maternal aunts and maternal grandmother. On the paternal side, her father, two uncles and a grandfather all had a history of learning difficulties/dyslexia.

On examination, she had a height of 155 cm (10th percentile) and body mass index of 30.8 kg/m². Several distinctive facial features were identified including a round face, low anterior hairline, a short philtrum, unusual-looking ears, and prominent upper central incisors (Figure 1). She had noticeably short 4th and 5th fingers and toes (Figure 2). She also had leg length difference with her right femur being 1 cm shorter than the left. Two faint, irregularly shaped café-au-lait macules were noted on her right inner arm and back.

Investigations revealed a low 25-hydroxy-vitamin D level of 22 nmol/L and she was advised to take vitamin D supplements. Other biochemistry and hormonal profiles were normal (Table 1). Her bone mineral density was within normal limits. X-ray confirmed variably shortened fifth metacarpal and fourth metatarsal bones bilaterally with no subcutaneous calcifications (Figure 3). Apart from the initial suggestion of advanced bone age at a chronological age of 10 years, subsequent skeletal survey performed at age 12 years was reported to be normal, with no ectopic ossifications. She had a normal karyotype and normal FISH of 2q37.2 chromosomal region.
Fig 1: Photograph taken at age 8.5 years revealed macrodontia of the upper central incisors

Fig 2: Brachydactyly, with a short left 5th metacarpal and a short left 4th metatarsal. A “dimple” sign can be seen due to the shortened metacarpal.
Fig 3: Xray showing the shortened metacarpal and metatarsal bones

<table>
<thead>
<tr>
<th>Table 1: Biochemistry and hormonal profiles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Result</strong></td>
</tr>
<tr>
<td><strong>Reference range</strong></td>
</tr>
<tr>
<td>Serum calcium 2.51 mmol/L</td>
</tr>
<tr>
<td>2.10-2.60</td>
</tr>
<tr>
<td>Serum phosphorus 0.75 mmol/L</td>
</tr>
<tr>
<td>0.75-1.50</td>
</tr>
<tr>
<td>Thyroid stimulating hormone 1.8 mIU/L</td>
</tr>
<tr>
<td>0.5-4.0</td>
</tr>
<tr>
<td>Intact parathyroid hormone 3.1 pmol/L</td>
</tr>
<tr>
<td>1.5-9.9</td>
</tr>
<tr>
<td>25(OH) vitamin D 22 nmol/L</td>
</tr>
<tr>
<td>51-200</td>
</tr>
<tr>
<td>Type 1 procollagen (P1NP) 44 ng/mL</td>
</tr>
<tr>
<td>15-90</td>
</tr>
<tr>
<td>Prolactin 145 mIU/L</td>
</tr>
<tr>
<td>40-570</td>
</tr>
<tr>
<td>Cortisol (AM) 254 nmol/L</td>
</tr>
<tr>
<td>AM 120-620, PM 100-400</td>
</tr>
<tr>
<td>Adrenocorticotropic hormone 5.0 pmol/L</td>
</tr>
<tr>
<td>&lt;11</td>
</tr>
<tr>
<td>Growth hormone 2.7 mIU/L</td>
</tr>
<tr>
<td>&lt;18</td>
</tr>
<tr>
<td>Insulin-like growth factor-1 30 nmol/L</td>
</tr>
<tr>
<td>13-41</td>
</tr>
</tbody>
</table>

Her pattern of bony anomalies fell into the classification of Brachydactyly Type E and the syndromic causes of which, in association with short stature and developmental delay, were considered and summarised in Table 2. Due to the wide differentials and the lack of a commercial gene panel that would cover all differential diagnoses, whole genome sequencing (WGS) was arranged. WGS with genome-wide analysis identified a
heterozygous frameshift mutation in the \textit{ANKRD11} gene (c.3045del, p.(Asp1016Ilefs*302)). This was confirmed to be a de novo mutation, as neither parent carried the mutation. This variant is associated with KBG syndrome (OMIM #148050) and has been classified as a pathogenic (class 5) variant based on the ACMG criteria [1]. The patient provided consent for the publication of her case.

\textbf{Discussion}

This young woman presented with brachydactyly type E, distinctive facies, leg length discrepancy, and mild intellectual impairment. The skeletal anomalies provided important clues, based on which the differential diagnoses were derived.

Brachydactyly is classified into several types, depending on the affected digit and the topography of the shortened bone within the digit [2]. Based on Temtamy’s classification in 1978, our patient demonstrated brachydactyly type E, which is characterised by shortened metacarpals +/- metatarsals. Brachydactyly type E may be an isolated occurrence, or could be part of a syndrome as such Turner syndrome, 2q37 microdeletion syndrome (a.k.a brachydactyly with mental retardation syndrome), or Albright Hereditary Osteodystrophy (AHO) with/without hormone resistance [3]. Pseudopseudohypoparathyroidism (PPHP) was considered based on her AHO features, including short stature, shortened 4\textsuperscript{th}/5\textsuperscript{th} metacarpals/metatarsals, a round face, and mild intellectual impairment, with absence of hormone resistance. Other less likely differential diagnoses were considered, including acrodysostosis type 2, due to its overlapping features of short stature, elevated body mass index, brachydactyly (albeit being more generalised in acrodysostosis), advanced bone age, and developmental delay. McCune-Albright syndrome was considered in light of the café-au-lait macules albeit in atypical distribution, and lower limb asymmetry, the latter thought to be reminiscent of somatic mosaicism that is known to be the pathogenic mechanism of this condition. Although our patient does not have the characteristic fibrous dysplasia, the presentation of McCune-Albright syndrome can vary widely, depending on the stage at which post-zygotic mutations occur [4]. Table 2 summarises the shared features of these conditions.

Turner syndrome and 2q37 microdeletion syndrome were excluded based on the normal karyotype and normal 2q37.2 FISH results, respectively. WGS did not identify any clinically significant variant in the \textit{GNAS}, \textit{PRKARIA}, or \textit{PDE4D} genes. The patient was found to have a heterozygous loss-of-function mutation in exon 10 of the \textit{ANKRD11} gene, associated with KBG syndrome.

\textit{ANKRD11} gene is located on chromosome 16 and encodes for the protein Ankyrin repeat domain-containing protein 11, which functions as a nuclear co-regulator and regulates neurogenesis in the embryonic brain [5]. It recruits histone deacetylases (HDACs), resulting in the inhibition of ligand-dependent transcriptional activation [6]. One of these HDACs, HDAC4, regulates genes involved in bone, muscle, and neurological development. Indeed, haploinsufficiency of HDAC4 has been identified to be the critical mechanism that
determines the AHO-like phenotype of 2q37 microdeletion syndrome [7]. The association between ANKRD11 and HDAC4 may explain some of the shared features between 2q37 microdeletion syndrome and KBG syndrome, such as short stature, brachydactyly, and developmental delay.

KBG syndrome is named after the initials of the last names of three original families reported in 1975. There have been over 100 patients reported in the literature, but the actual prevalence is not known, and perhaps under-reported because of the variable presentation that can often be mild [8]. It is an autosomal dominant condition characterised by short-stature (height <3rd percentile), macrodontia of the central upper incisors, distinctive facial features and learning difficulties [9]. In a series of 32 KBG patients from 27 families, the most universal findings were speech delay and learning difficulties [10]. Macrodontia of the upper central incisors was seen in 85%, and 43% had seizures with onset varying between infancy to mid-teens [10]. Short stature (<3rd percentile) was a feature in 40% of the patients and brachydactyly, especially of the 5th finger with striking clinodactyly, were the most consistent features. Delayed bone age was also a feature of KBG syndrome. Since the initial clinical description in 1975 and the subsequent identification of the ANKRD11 gene in association with KBG syndrome in 2011 [12], several diagnostic criteria have been proposed [13, 14] and subsequent revisions to the criteria have been suggested [10, 15].

The diagnosis of KBG syndrome was unexpected in our patient, as her facial phenotype was different, and she had advanced, rather than delayed, bone age. In retrospect, this diagnosis explains many of her other features, including short stature (height on the 10th percentile), brachydactyly, prominent upper central incisors which was retrospectively appreciated, and mild learning difficulties. Indeed, a recent Australian study of 18 KBG syndrome cases (16 with confirmed ANKRD11 gene mutation), whilst reporting a lower incidence of seizures (16.7%), supported the removal of the bone age criteria, and proposed potential revisions to account for stature which can range from short (<10th percentile) to normal stature [15]. Furthermore, it has been suggested that KBG syndrome is more common than is recognised, as adult relatives are increasingly diagnosed retrospectively after their children’s diagnosis, especially as the use of whole exome/genome sequencing becomes more prevalent.

**Conclusion**

We present the case of a young woman with brachydactyly type E and other features resembling AHO. WGS, that excluded syndromes associated with AHO, identified a de novo heterozygous pathogenic mutation in the ANKRD11 gene, associated with KBG syndrome. Had targeted genetic testing been undertaken, the definitive diagnosis may not have been reached. KBG syndrome is likely to be more common than is recognised due to the variable and often mild phenotype. We suggest that KBG syndrome should be considered in the differential diagnosis of syndromic brachydactyly type E, especially if short stature and developmental delay are also present.
Table 2: Differential diagnoses of syndromes associated with brachydactyly type E

<table>
<thead>
<tr>
<th>Patient</th>
<th>Brachydactyly</th>
<th>Short stature</th>
<th>Obesity</th>
<th>Developmental delay</th>
<th>Facial dysmorphism</th>
<th>Bone age</th>
<th>Hormone resistance</th>
<th>Other features</th>
<th>Genetic basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>KBG syndrome</td>
<td>+ (type E reported); more consistently 5th finger clinodactyly</td>
<td>+ (postnatal onset)</td>
<td>-</td>
<td>+ (mild)</td>
<td>Triangular face, long philtrum, hypertelorism, low anterior hairline, macrodontia</td>
<td>Delayed</td>
<td>-</td>
<td>Macrodontia of the upper central incisor, congenital cardiac anomaly</td>
<td>Heterozygous LOF mutation in ANKR11 gene</td>
</tr>
<tr>
<td>Acrodyostosis type 2</td>
<td>+ (generalised)</td>
<td>+ (variable)</td>
<td>+</td>
<td>+ (mild-moderate)</td>
<td>Maxillary and nasal hypoplasia, hypertelorism, low-set ears, epicanthic folds</td>
<td>Advanced</td>
<td>+ (type 1)</td>
<td>Cone-shaped epiphyses, vertebral anomaly</td>
<td>Heterozygous GOF mutation in PRKAR1A (type 1); or missense mutation in PDE4D (type 2)</td>
</tr>
<tr>
<td>2q37 microdeletion syndrome</td>
<td>+ (type E)</td>
<td>+ (+)</td>
<td>± (± autism)</td>
<td>Round facies, sparse hair/eyebrow, upslanting palpebral fissures, midface hypoplasia</td>
<td>N/A</td>
<td>-</td>
<td>Hypotonia, joint hypermobility, scoliosis</td>
<td>Heterozygous deletion of chromosomal region 2q37 involving HDAC4 gene</td>
<td></td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Posteriorly-rotated ears, webbed neck, low posterior hairline</td>
<td>Normal</td>
<td>-</td>
<td>Primary hypogonadism, congenital cardiac defect, skeletal/renal anomalies</td>
<td>Chromosomal aneuploidy 45,XO</td>
<td></td>
</tr>
<tr>
<td>McCune Albright syndrome</td>
<td>-</td>
<td>N/A</td>
<td>N/A</td>
<td>-</td>
<td>Craniofacial expansile deformities</td>
<td>N/A</td>
<td>-</td>
<td>Characteristic café-au-lait macules that respect the midline or follow Lines of Blaschko, precocious puberty, fibrous dysplasia, scoliosis, excessive production of endocrine hormones</td>
<td>Postzygotic somatic GOF mutation in GNAS gene</td>
</tr>
</tbody>
</table>

LOF – loss of function; GOF – gain of function
References


